

Can we help patients with the oral allergy syndrome eat fresh fruit?

A double blind placebo controlled randomised trial to study the effects of birch pollen specific immunotherapy (BP-SIT) on the symptoms of oral allergy syndrome in adult patients

Statistical Analysis

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1. Abbreviations

Abbreviation	Meaning
CPT	Conjunctival Provocation Test
DBPCFC	Double Blind Placebo Controlled Food Challenge
SPT	Skin Prick Test
VAS	Visual Analogue Score
Y0/Y1/Y2	Year 0 (baseline)/Year 1/Year 2

2. Participant demographics

Table 1: Participant demographics at baseline.

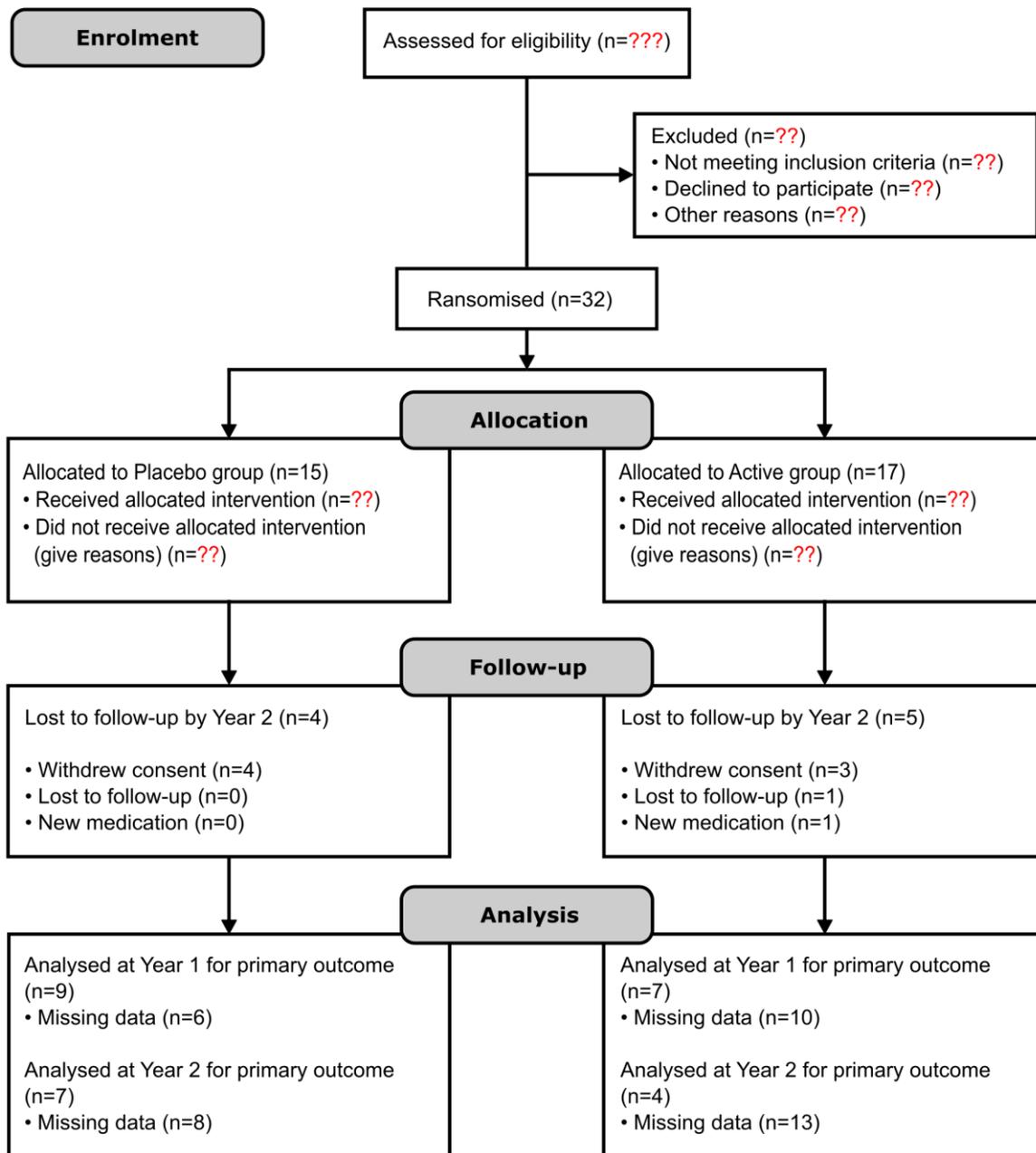
	Group					
	Active (n=17)		Placebo (n=15)		Overall (n=32)	
	Mean	SD	Mean	SD	Mean	SD
Age	40.7	12.4	38	10.3	39.4	11.4
	No.	%	No.	%	No.	%
Male	3	18	4	27	7	22
Female	14	82	11	73	25	78

3. Withdrawals

Table 2: Withdrawals and reasons for withdrawal

	Group					
	Active (n=17)		Placebo (n=15)		Overall (n=32)	
	No.	%	No.	%	No.	%
Did not withdraw	12	71	11	73	23	72
Withdrew from study	5	29	4	27	9	28
Total	17	100	15	100	32	100
Reason if withdrawn						
Withdrew consent	3	60	4	100	7	78
Lost to follow up	1	20	0	0	1	11
New medication	1	20	0	0	1	11
Total	5	100	4	100	9	100

Figure 1: CONSORT diagram



4. Outcome summaries at each time point

Table 3: Primary and Secondary outcome summaries at baseline.

	Group								
	Active			Placebo			Overall		
	No.	%		No.	%		No.	%	
Apple DBPCFC threshold									
0	1	6		0	0		1	3	
3	6	35		7	47		13	41	
10	3	18		3	20		6	19	
30	2	12		3	20		5	16	
100	1	6		1	7		2	6	
999	4	24		1	7		5	16	
Total	17	100		15	100		32	100	
CPT threshold									
50	0	0		1	7		1	3	
160	4	24		5	33		9	28	
500	7	41		5	33		12	38	
1600	6	35		4	27		10	31	
5000	0	0		0	0		0	0	
Total	17	100		15	100		32	100	
	Median	IQR	n	Median	IQR	n	Total	IQR	n
SPT Grass	5.5	5.0-7.0	17	6.0	4.0-7.0	15	5.5	4.0-7.0	32
SPT Early tree	7.5	7.0-9.5	17	6.5	6.0-9.0	15	7.5	6.5-9.3	32
SPT Mid tree	8.5	7.5-9.5	17	7.0	6.0-9.0	15	8.0	6.8-9.3	32
SPT Birch	9.0	7.5-10.0	17	9.0	7.5-10.0	15	9.0	7.5-10.0	32
SPT Apple sap	5.0	4.5-7.0	17	5.5	5.0-8.5	15	5.5	5.0-7.3	32
SPT Apple commercial	0.0	0.0-0.0	17	0.0	0.0-0.0	15	0.0	0.0-0.0	32
Apple VAS	60.0	40.0-70.0	17	50.0	45.0-80.0	15	60.0	42.5-74.0	32

Table 4: Primary and Secondary outcome summaries at Year 1

	Group								
	Active			Placebo			Overall		
	No.	%		No.	%		No.	%	
Apple DBPCFC threshold									
0	0	0		0	0		0	0	
3	2	29		2	22		4	25	
10	2	29		4	44		6	38	
30	3	43		3	33		6	38	
100	0	0		0	0		0	0	
999	0	0		0	0		0	0	
Total	7	100		9	100		16	100	
CPT threshold									
50	0	0		2	15		2	8	
160	1	8		1	8		2	8	
500	1	8		5	39		6	24	
1600	7	58		4	31		11	44	
5000	3	25		1	8		4	16	
Total	12	100		13	100		25	100	
	Median	IQR	n	Median	IQR	n	Median	IQR	n
SPT Grass	6.0	4.0-9.0	13	6.3	5.0-6.5	14	6.0	4.0-8.0	27
SPT Early tree	7.0	6.0-10.0	13	7.5	6.0-8.0	14	7.5	6.0-9.0	27
SPT Mid tree	7.0	6.5-8.5	13	8.3	7.0-9.5	14	8.0	6.5-9.5	27
SPT Birch	7.5	6.5-8.0	13	8.5	6.0-9.0	14	8.0	6.5-9.0	27
SPT Apple sap	5.0	4.0-6.5	13	5.3	4.0-7.0	14	5.0	4.0-7.0	27
SPT Apple commercial	0.0	0.0-2.0	13	0.0	0.0-1.5	14	0.0	0.0-2.0	27
Apple VAS	37.5	30.0-65.0	10	50.0	30.0-60.0	13	30	30.0-65.0	23

Table 5: Primary and Secondary outcome summaries at Year 2

	Group								
	Active			Placebo			Overall		
	No.	%		No.	%		No.	%	
Apple DBPCFC threshold									
0	1	25		0	0		1	9	
3	0	0		2	29		2	18	
10	2	50		2	29		4	36	
30	0	0		2	29		2	18	
100	1	25		0	0		1	9	
999	0	0		1	14		1	9	
Total	4	100		7	100		11	100	
CPT threshold									
50	0	0		0	0		0	0	
160	0	0		0	0		0	0	
500	1	17		2	25		3	21	
1600	3	50		4	50		7	50	
5000	2	33		2	25		4	29	
Total	6	100		8	100		14	100	
	Median	IQR	n	Median	IQR	n	Median	IQR	n
SPT Grass	4.0	2.0-6.5	11	4.5	3.5-6.0	10	4.0	2.0-6.0	21
SPT Early tree	5.0	5.0-8.5	11	6.8	5.0-10.0	10	6.0	5.0-8.5	21
SPT Mid tree	6.3	5.0-8.0	10	8.0	7.5-8.5	10	7.8	6.0-8.5	20
SPT Birch	6.0	4.0-9.0	11	6.5	4.6-8.5	10	6.0	4.5-8.5	21
SPT Apple sap	4.0	1.0-4.0	11	4.0	3.0-4.0	10	4.0	3.0-4.0	21
SPT Apple commercial	0.0	0.0-2.0	9	0.0	0.0-1.0	8	0.0	0.0-2.0	17
Apple VAS	15.0	0.0-20.0	9	15.0	10.0-20.0	7	15.0	2.5-20.0	16

5. Primary analyses

The 'Apple DBPCFC threshold' was converted to 'Apple DBPCFC threshold level' for each year. The change in level was calculated for year 1 and year 2 as Year 1 or 2 - Year 0. A negative change indicates a higher threshold at Year 0 and therefore a worse outcome at year 1/2. A positive change indicates a higher threshold at Year 1 or 2 and therefore a positive outcome.

Mann-Whitney tests were used to test the null hypotheses that the differences in changes between year 1/2 and year 0 were the same for both the active and placebo groups.

Table 6: Comparisons of apple DBPCFC threshold level year 1 - year 2 change and year 2 - year 0 change between active and placebo groups.

Apple DBPCFC threshold Y1-Y0 difference			
Group	n	rank sum	p value
Active	7	69.5	
Placebo	9	66.5	0.276
Apple DBPCFC threshold Y2-Y0 difference			
Group	n	rank sum	p value
Active	4	25.0	
Placebo	7	41.0	0.843

There is insufficient evidence to reject the null hypothesis of no difference between active and placebo groups for either the change from year 0 to year 1, or year 0 to year 2.

6. Secondary analyses

6.1 CPT threshold changes

The 'Conjunctival Provocation Test threshold' was converted to 'Conjunctival Provocation Test threshold level' for each year. The change in level was calculated for year 1 and year 2 as Year 1 or 2 - Year 0. A negative change indicates a higher threshold at Year 0 and therefore a worse outcome at year1/2. A positive change indicates a higher threshold at Year 1 or 2 and therefore a positive outcome.

Mann-Whitney tests were used to test the null hypothesis that the differences in changes between year 1/2 and year 0 were the same for both the active and placebo groups.

Table 7: Comparisons of CPT threshold level year 1 - year 2 change and year 2 - year 0 change between active and placebo groups.

CPT threshold Y1-Y0 difference			
Group	n	rank sum	p value
Active	12	175.5	
Placebo	13	149.5	0.269
CPT threshold Y2-Y0 difference			
Group	n	rank sum	p value
Active	6	38.0	
Placebo	8	67.0	0.326

There is insufficient evidence to reject the null hypothesis of no difference between active and placebo groups for either the change from year 0 to year 1, or year 0 to year 2.

6.2 SPT changes

For each SPT variable, the change was calculated for year 1 and year 2 as Year 1 or 2 - Year 0. A negative change indicates a higher SPT result at Year 0 and therefore a positive outcome at year 1/2. A positive change indicates a higher SPT result at Year 1 or 2 and therefore a negative outcome.

T-tests were used to test the null hypotheses that the mean differences in changes between year 1/2 and year 0 were the same for both active and placebo groups.

Table 8: Comparisons of SPT year 1 - year 2 change and year 2 - year 0 change between active and placebo groups.

SPT Grass Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	0.31	3.31	-1.69	2.31	
Placebo	14	0.14	2.58	-1.34	1.63	
Difference (Active-Placebo)		0.16		-2.17	2.50	0.8858
SPT Grass Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	11	-1.55	5.06	-4.94	1.85	
Placebo	10	-0.25	2.24	-1.85	1.35	
Difference (Active-Placebo)		-1.30		-4.93	2.34	0.4653
SPT Early tree Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	-1.12	4.14	-3.62	1.39	
Placebo	14	0.32	2.55	-1.15	1.80	
Difference (Active-Placebo)		-1.44		-4.14	1.27	0.2845
SPT Early tree Y2-Y1 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	11	-2.59	4.53	-5.63	0.45	
Placebo	10	0.40	2.50	-1.39	2.19	
Difference (Active-Placebo)		-2.99		-6.38	0.40	0.0806
SPT Mid tree Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	-1.92	2.64	-3.52	-0.33	
Placebo	14	1.21	2.69	-0.34	2.77	
Difference (Active-Placebo)		-3.14		-5.25	-1.02	0.0052
SPT Mid tree Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	10	-3.85	3.46	-6.33	-1.37	
Placebo	10	1.85	3.76	-0.84	4.54	
Difference (Active-Placebo)		-5.70		-9.10	-2.30	0.0024

Table 8: Comparisons of SPT year 1 - year 2 change and year 2 - year 0 change between active and placebo groups (cont.).

SPT Birch Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	-2.15	2.30	-3.55	-0.76	
Placebo	14	-0.93	2.32	-2.27	0.41	
Difference (Active-Placebo)		-1.23		-3.06	0.61	0.181
SPT Birch Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	11	-2.73	4.22	-5.56	0.11	
Placebo	10	-1.70	4.31	-4.78	1.38	
Difference (Active-Placebo)		-1.03		-4.93	2.87	0.5877
SPT Apple sap Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	-0.31	3.58	-2.47	1.86	
Placebo	14	-1.21	3.38	-3.16	0.74	
Difference (Active-Placebo)		0.91		-1.85	3.66	0.5046
SPT Apple sap Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	11	-2.45	2.50	-4.14	-0.77	
Placebo	10	-4.10	4.47	-7.30	-0.90	
Difference (Active-Placebo)		1.65		-1.62	4.91	0.3052
SPT Apple commercial Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	13	0.73	1.13	0.05	1.41	
Placebo	14	0.43	1.24	-0.29	1.14	
Difference (Active-Placebo)		0.30		-0.64	1.24	0.5147
SPT Apple commercial Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	9	0.83	1.37	-0.22	1.89	
Placebo	8	0.75	1.49	-0.49	1.99	
Difference (Active-Placebo)		0.08		-1.39	1.56	0.9059

There is insufficient evidence to reject the null hypothesis of no difference between the active and placebo groups for either the change from year 0 to year 1, or year 0 to year 2 for any of the SPT variables, except for SPT Mid tree.

For SPT Mid tree there is strong evidence against the null hypothesis of no difference between the active and placebo groups for both year 0 to year 1 and year 0 to year 2.

The difference in mean change between groups (Active - Placebo) for year 0 to year 1 is 3.14 (95% CI: -5.25 to -1.02), indicating improvement in the Active group.

The difference in mean change between groups (Active - Placebo) for year 0 to year 2 is 5.70 (95% CI -9.10 to -2.3), indicating improvement in the Active group.

6.3 VAS changes

The change in VAS was calculated for year 1 and year 2 as Year 1 or 2 - Year 0. A negative change indicates a higher VAS result at Year 0 and therefore positive outcome. A positive change indicates a higher SPT result at Year 1 or 2 and therefore a negative outcome.

T-tests were used to test the null hypothesis that the mean differences in changes between year 1/2 and year 0 were the same for the active and placebo groups.

Table 9: Comparisons of apple VAS year 1 - year 2 change and year 2 - year 0 change between active and placebo groups.

VAS Y1-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	10	-20.30	26.89	-39.54	-1.06	
Placebo	13	-15.38	24.36	-30.11	-0.66	
diff		-4.92		-27.20	17.37	0.6512
VAS Y2-Y0 difference						
Group	n	Mean	Std. Dev.	Lower 95% CI	Upper 95% CI	p-value
Active	9	-43.11	4.57	-46.62	-39.60	
Placebo	7	-32.86	19.76	-51.13	-14.58	
diff		-10.25		-24.73	4.22	0.1509

There is insufficient evidence to reject the null hypothesis of no difference between the active and placebo groups for either the change from year 0 to year 1, or year 0 to year 2.

7. Appendix 1: Subset of variables for analysis and derived variables

Variable name	Variable type	Range/categories	Description
Randno	String		Participant ID
Group	Binary	1=active 2=placebo	Intervention group
Age	Continuous	>0	Age (years)
Sex	Binary	1=Male 2=Female	Gender (1=Male, 2=Female)
VASY0/1/2	Continuous	0-100	VAS scores
DBFCY0/1/2	Ordinal	0=Placebo 3 10 30 100 999=Above threshold	Apple DBFCY threshold Y0/1/2 (grams, primary outcome)
DBFCY0/1/2_l	Ordinal	0=0 1=3 2=10 3=30 4=100 5=999	Apple DBFCY threshold level Y0/1/2
SPTGY0/1/2	Continuous	≥0	SPT grass Y0/1/2
SPTEY0/1/2	Continuous	≥0	SPT early tree Y0/1/2
CPTY0/1/2	Ordinal	50 160 500 1600 5000	CPT threshold Y0/1/2
CPTY0/1/2_l	Ordinal	1=50 2=160 3=500 4=1600 5=5000	CPT threshold level Y0/1/2
SPTMY0/1/2	Continuous	≥0	SPT mid tree Y0/1/2
SPTBY0/1/2	Continuous	≥0	SPT birch Y0/1/2
SPTAY0/1/2	Continuous	≥0	SPT apple sap Y0/1/2
SPTCY0/1/2	Continuous	≥0	SPT apple commercial Y0/1/2
WDATE	String		Withdrawal date
WREASON	Categorical	1=Withdrew consent 2=Lost to follow up 3=New medication	Withdrawal reason

For all variables except DBFCY0/1/2 and CPTY0/1/2, '999' indicates missing values.

For DBFCY0/1/2, '999' indicates a result over the measurable threshold and '888' indicates missing values.

For CPTY0/1/2, '9999' indicates missing values.